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"European Panel On Low Density Lipoprotein (LDL) Subclasses": A Statement on the Pathophysiology, Atherogenicity and Clinical Significance of LDL Subclasses: Executive Summary

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INTRODUCTION

Low density lipoproteins (LDL) comprise multiple subclasses with discrete size and density, different physicochemical composition and metabolic behaviour. Ultracentrifugation and electrophoretic techniques have identified up to 7 distinct LDL subclasses. It has been suggested that there are parallel metabolic channels within the de-lipidation cascade from very-low density lipoprotein (VLDL) to LDL and a metabolic relationship between large VLDL particles and small LDL particles has been demonstrated using stable isotopes in subjects with a predominance of small dense (sd) LDL. These studies have not yet identified the specific precursors of individual LDL subclasses. However, data from animal models suggest that separate pathways may be responsible for the generation of distinct LDL particles. Further, dietary intervention studies have shown inverse associations between changes in large and small LDL, as well as between changes in medium sized and very small LDL which raise the possibility of precursor-product relationships between distinct LDL subclasses.

The activity of lipolytic enzymes has been linked to LDL size: reduced lipoprotein lipase (LpL) activity and increased hepatic lipase (HL) activity have been shown in subjects with a predominance of sdLDL. Elevated plasma triglycerides (TGs) seem to be the main determinant of LDL subclass distribution. Indeed, the formation of sdLDL particles is mostly observed in hypertriglyceridaemic state, a condition that promotes an increased transfer of TGs from TG-rich lipoproteins to LDL and high density lipoprotein (HDL) particles in exchange of cholesterol esters (CE) through the action of cholesterol ester transfer protein (CETP). These processes lead to the generation of VLDL particles enriched in CE and smaller, TG-rich LDL particles that are good substrates for HL. As a consequence, the value of sdLDL as a predictor of vascular risk is usually reduced when TG levels are taken into account. Future studies on diet-gene interactions affecting LDL subclasses may contribute to the understanding of mechanisms underlying the inter-individual variability in LDL subclass distribution.

CLINICAL EVIDENCE FOR THE SIGNIFICANCE OF sdLDL

Several lines of evidence suggest that the quality of LDL influences cardiovascular risk. To date, the magnitude and independence of the association of sdLDL with cardiovascular disease (CVD) has been tested in more than 50 studies, including cross-sectional and prospective epidemiologic as well as clinical intervention trials. The majority of these trials demonstrate a significant association of sdLDL with increased CVD risk. Several mechanisms have been proposed to explain the enhanced atherogenicity of sdLDL. sdLDL may infiltrate arterial tissue more easily than larger LDL. In

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addition, smaller LDL particles may have decreased receptor-mediated uptake into cells, and express increased affinity for proteoglycan. Furthermore, oxidative susceptibility increases and antioxidant capacity is diminished with decreasing LDL size. Altered properties of the surface lipid layer associated with a reduced content of free cholesterol and increased content of polyunsaturated fatty acids might contribute to enhanced oxidative susceptibility of sdLDL.

Increased levels of sdLDL are a feature of subjects at very-high CVD risk, such as those with coronary heart disease (CHD) and type 2 diabetes, as well as those with clinical forms of non-coronary atherosclerosis. Furthermore, recent studies have suggested that sdLDL may be a marker for the diagnosis and severity of the metabolic syndrome. Finally, evidence from angiographic clinical trials indicates that treatment benefit was related to a decrease in sdLDL particles. These studies include the St. Thomas Atherosclerosis Regression Study (STARS), the Monitored Atherosclerosis Regression Study (MARS), the Stanford Coronary Risk Intervention Project (SCRIP) and the Familial Atherosclerosis Treatment Study (FATS).

MEASUREMENT OF SMALL DENSE LDL

In view of the technical difficulties in establishing the 'best' method for separating LDL subclasses in terms of analytical and diagnostic performance, the choice of method will depend, to a large extent, on the availability of equipment, expertise to run and interpret the test and the specific experimental requirements. Under these considerations, the techniques fall into 3 categories. The bench or 'reference' methods of analytical and density gradient ultracentrifugation and gradient gel electrophoresis that provide high resolution have low throughput and are labour intensive. Alternatively, if large cohorts of samples need to be analysed without the facility of a laboratory or cost restraints, then the commercial companies, LipoScience© (nuclear magnetic resonance assay), Berkeley HeartLab© (gradient gel electrophoretic assay) or Atherotech© (ultracentrifugation assay) all provide reliable and standardised services. Finally, if the aim is to establish an 'in-house' method with high throughput and an acceptable degree of standardisation, then the commercially available tests such as LipoPrint© (gradient gel electrophoretic assay) or the newer precipitation assay for sdLDL (differential precipitation assay), both represent viable options.

EFFECTS OF TREATMENT ON sdLDL LEVELS

This document considers the effect of lipid lowering drugs as well as other pharmacological interventions on sdLDL. The effects of lifestyle measures are also discussed.

CONCLUSIONS

There is considerable evidence that sdLDL contribute to the pathogenesis of atherosclerosis and accelerate its progression. Further work is required to provide simpler faster assays for sdLDL and also to standardise these assays. Indeed, there is still no universal agreement on what represents the reference or 'gold' standard for the assessment of LDL subclasses. Each method determines different characteristics of the LDL particles (e.g. density, size, electrophoretic mobility), thus complicating the interpretation of studies that have used different methods.

Measurement of sdLDL may have a role in clinical practice in the monitoring of patients with hypertriglyceridaemia beyond that provided by LDL-cholesterol and possibly also non-HDL-cholesterol and apolipoprotein B. There is a need to establish the clinical relevance of decreasing sdLDL fractions selectively with little effect on the buoyant fractions vs decreasing all fractions to a similar extent. The latter situation (e.g. using a statin) would reduce total LDL-cholesterol more considerably than a fibrate (a drug class which would more specifically target sdLDL). All these effects may depend on the population studied, their baseline lipid profile and the drug (and dose) used.

The reference for complete text of the consensus statement is [1].

REFERENCE

[1] Mikhailidis DP, Elisaf M, Rizzo M, *et al.* European Panel on Low Density Lipoprotein (LDL) Subclasses: a statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses. Curr Vasc Pharmacol 2011; 9: 533-71.